American Journal of Hematology 58:142–144 (1998)

Acute Renal Failure Precipitated by Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in Multiple Myeloma

Ethan Yussim, Eli Schwartz, Yechezkel Sidi, and Michael Ehrenfeld*

Chaim Sheba Medical Center, Tel-Hashomer, Israel

INTRODUCTION

Multiple myeloma (MM) is a malignant proliferation of plasma cells, resulting from a single clone. Typical clinical features are bone pain, fractures, renal failure, susceptibility to infection, anemia, hypercalcemia, clotting disorders, neurological symptoms, and hyperviscosity syndromes [1,2]. Clinical manifestations vary from patient to patient. Renal failure occurs in about 20–25% of MM patients, but more than half of all myeloma patients show some renal abnormalities [1].

We describe three MM patients whose clinical presentation was acute renal failure precipitated by nonsteroidal anti-inflammatory drugs (NSAIDs), including the one reported by us earlier [3], as well as discuss two similar cases described by Wu and colleagues in 1987 [4]. We suggest that treatment with NSAIDs in patients with MM should be reconsidered, due to the risk of developing or aggravating renal failure.

PATIENTS

Patient 1

A 62-year-old woman with light chain MM, osteolytic lesions, and hypercalcemia received 1,000 mg of naproxen per day, for myeloma-associated fever. Ten days after the initiation of this therapy, the patient developed multiple myoclonic jerks. She was found to have laboratory signs of acute renal failure, with a blood urea nitrogen (BUN) of 265 mg/dL, hyperkalemia, and hypercalcemia. Her body temperature was normal. One hour after arriving at the emergency room, the patient developed severe pulmonary insufficiency and died a short time later. A postmortem examination revealed precipitation of large hyaline casts around renal tubular cells, which were identified by immunoperoxidase staining as lambda light chains. Also found in the kidney were small foci of plasma cells. Bone marrow examination showed massive replacement by atypical plasma cells, positive for monoclonal lambda light chains [3].

Patient 2

A 66-year-old woman was admitted because of increased weakness. A serum creatinine of 4.9 mg%, proteinuria and sterile pyuria were found. She received diclofenac 50–150 mg daily for the last 8 weeks, because of increasing bone pain. Interstitial nephritis due to therapy, with NSAIDs was initially diagnosed. The creatinine levels decreased slowly; however, weakness and bone pain continued. She was therefore referred to hospital. Upon admission the serum creatinine was already 1.9, and the BUN 22.5 mg/Dl. Further, a normochromic normocytic anemia was found. Radiographic study of the skull showed punched-out lesions, and a chest X-ray revealed a compressed fracture of the twelfth thoracic vertebra. Bone marrow biopsy showed massive replacement of the normal marrow with pathologic plasma cells. Ten days after initiation of treatment with combination chemotherapy, the patient's renal functions returned to normal.

Patient 3

A 74-year-old woman was admitted to hospital because of general deterioration. Serum creatinine was found to be 10.0 mg/dL, BUN 112.5 mg/dL. Hyperkalemia of 6.2 mmol/L and an anemia were also found. She received intramuscular injections of sodium diclofenac during the previous week (total dose 450 mg). Skeletal radiographic studies showed multiple punched-out lesions. Serum protein electrophoresis demonstrated an elevated monoclonal IgA-kappa fraction. Urine protein electrophoresis revealed an abnormal peak of 66% between the beta and gamma globulin. The bone marrow biopsy showed replacement of the normal tissue by

*Correspondence to: Dr. M. Ehrenfeld, Dept. of Medicine C, Chaim Sheba Medical Center, Tel-Hashomer, 52621, Israel.

Received for publication 28 May 1997; Accepted 27 June 1997

plasma cells. Nine days after initiation of therapy, which included five sessions of hemodialysis and high dose intravenous dexamethasone, her renal function improved, with reduction of the serum creatinine level to 1.8 mg/dL and the BUN to 73 mg/dL, though the patient was still oliguric. The patient remained on chronic hemodialysis.

DISCUSSION

MM is a malignant proliferation of plasma cells of unknown etiology. The incidence of MM tends to rise with age, with the median age around 60 years [2]. The annual incidence is 4 per 100,000, similar in various countries around the world. MM is twice as prevalent in blacks than in whites, and males are slightly more affected than females.

The clinical manifestations vary from patient to patient. The skeletal system is the most commonly affected, due to increased osteoclastic activity. Bone pain is present in nearly 70% of patients. Other manifestations of MM in the skeletal system include osteoporosis with typical radiological findings and pathologic fractures. Susceptibility to bacterial infections, especially by *Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae,* and *Escherichia coli,* due to defects in many components of the humoral and cellular immune systems, is also typical.

Renal failure occurs in 25–50% of MM patients, but in more than half of all myeloma patients there is some renal abnormality [5]. Other common clinical manifestations include anemia and hypercalcemia. Rare clinical manifestations of MM include clotting abnormalities, neurological symptoms, and hyperviscosity.

The most common causes for renal failure in MM are hypercalcemia and the deposition of light chain proteins in renal tubular cells, mainly in the basement membranes of the glomeruli and tubuli, in complex with calcium. The pathophysiology of the tubulo-interstitial damage is dependent on the accumulation of light chain deposits in the tubuli, as well as a direct toxic damage. Lambda chains appear to be more nephrotoxic than kappa chains. Release of lysosomal content is also leading to the tubulo-interstitial damage.

This results in the typical ''myeloma kidney'': tubular cell atrophy, interstitial fibrosis, giant multi-nucleated cells, and intraluminal casts with intra-renal urinary obstruction [5].

Additional, less common causes for renal failure in MM are infiltration of the kidney with myeloma cells, deposition of amyloid, uric acid nephropathy, especially after chemotherapy, formation of calcium or uric acid calculi, and a decrease in renal blood flow due to hyperviscosity. Intravenous pyelograms can induce renal failure in MM patients, especially if they are dehydrated.

NSAIDs exert their therapeutic effect in man by inhibiting the production of prostaglandins (PGs) via inhibition or interference with the action of the enzyme cyclooxygenase (Cox1 and Cox2) [6]. By blocking the production of vasodilatory PGs, NSAIDs lead to a reduction in the renal blood flow and glomerular filtration rate, which can precipitate acute renal failure. However, evidence exists that the effect on the renal function occurs only in sodium-depleted individuals, as in patients with congestive heart failure, hepatic cirrhosis, chronic renal failure, or any other hypovolemic states [7,8].

Additional effects of NSAIDs on the kidney include salt and water retention through prevention of the PG-induced inhibition on the reabsorption of chloride and on the antidiuretic hormone, as well as hyperkalemia, caused by several mechanisms. Nephropathy (including papillary necrosis and chronic interstitial nephritis) is uncommonly associated with the use of NSAIDs, but is far more common with the abuse of mixtures of these agents [9].

MM can lead to the development of acute renal failure, and many cases of MM present as such. It is also well established that patients with MM are especially at risk of developing renal failure in certain conditions, as dehydration or while receiving contrast media [5].

NSAIDs can precipitate renal failure in a clinical setting in which there is a decrease in renal blood flow, such as congestive heart failure or other hypovolemic states. In cases of pre-existing renal insufficiency, the use of NSAIDs may lead to further damage [8,9]. However, MM was not considered in the past as one of the risk factors for the development of renal failure during treatment with NSAIDs. On the contrary, some use NSAIDs as a treatment for skeletal pain or non-infectious fever in MM. NSAIDs are rarely considered as sole contributors to acute renal failure.

We hereby describe two patients who presented with acute renal failure after receiving NSAIDs for musculoskeletal pains, and whose diagnosis turned out to be MM, and one MM patient who developed acute renal failure after receiving NSAIDs. Two similar patients were described by Wu and colleagues [4]: the first was a 76-year-old woman who took 500 mg of naproxen twice a day, for low back pain, and was admitted to hospital after 1 week of treatment, with laboratory evidence of renal failure, hyperkalemia, and proteinuria.

Free light chains were detected in the urine, and the serum protein immunoelectrophoresis as well as the bone marrow examination confirmed the diagnosis of MM. After 3 weeks of chemotherapy and hemodialysis, the patient's renal functions improved (Table I).

The second patient described was an 81-year-old woman who took 375 mg of naproxen three times a day for hip pain. She was found to have renal failure, hypocalcemia, and proteinuria, again, 1 week after initiation

TABLE I. Demographic and Clinical Data of Patients With Renal Failure Precipitated by NSAIDs*

Patient no.	1	2	3	4	5	Mean[a]
Age (years)	62	66	74	74	81	71.8
Sex	f	f	f	f	f	
NSAID treatment	Naproxen 1,000 mg/day	Diclofenac sodium	Diclofenac sodium 75 mg/day	Naproxen 1,000 mg/day	Naproxen 1,125 mg/day	
Duration of NSAID treatment (days)	10	42	6	7	7	14.6
Known MM	Yes	No	No	No	No	
Presenting signs or symptoms	Myoclonic jerks	Deterioration in renal functions, weakness	General deterioration	Deterioration in renal functions	Deterioration in renal functions	
Renal functions[b]	BUN 265[c]	BUN 52 creat. 5.1	BUN 112.5 creat. 10.0	BUN 150 creat. 11.3	BUN 74 creat. 8.0	
Treatment		Radiotherapy, combination chemotherapy	Hemodialysis, dexamethasone pulse therapy	Hemodialysis, chemotherapy	Combination chemotherapy	
Outcome	Death within 1 h of arrival	BUN 24.5, creat 1.3	BUN 73 creat. 1.8	Creat. 4.4	Creat. 1.8	

*f, female; BUN, blood urea nitrogen (mg/dL); Creat, creatinine (mg/dL).
[a]When possible to calculate.
[b]In admission.
[c]No further details available.

of treatment. Free lambda light chains were found in the urine, and the diagnosis of MM was strengthened by typical bone marrow and immunoelectrophoresis findings. Her renal functions improved considerably after 6 weeks of combination chemotherapy (Table I).

Knowing the mechanism of action of NSAIDs on the one hand, and the pathophysiology of the miscellaneous renal dysfunction in MM on the other, we propose that their effects on the kidney are additive if not synergistic. The combined effect of NSAIDs and the various renal injuries in MM could be attained through many different pathways: the reduction of renal blood flow through a blockade of the production of vasodilator PGs, as well as tubulo-interstitial damage due to light chain deposits, nephrotoxic effects of light chain proteins, and via kidney deposition of amyloid.

We suggest that treatment with NSAIDs in patients with MM should be reconsidered, due to the risk of developing or aggravating renal failure.

Many questions, such as the exact mechanism of damage, variations in effect between different types of NSAIDs, relations to dosage and duration of treatment, predisposition of females to damage, and others, still remain unsolved. More studies are, therefore, required in order to reach a final conclusion and to establish exact recommendations regarding treatment with NSAIDs in MM.

REFERENCES

1. Alexanian R, Barlogie B, Dixon D: Prognosis of asymptomatic multiple myeloma. Arch Int Med 148:1963–1965, 1988.
2. Barlogie B, Epstein J, Selvanayagam P, Alexanian R: Plasma cell myeloma: New biological insights and advances in therapy. Blood 73:865–79, 1989.
3. Shpilberg O, Douer D, Ehrenfeld M, Engelberg S, Ramot B: Naproxen-associated fatal acute renal failure in multiple myeloma. Nephron 55:448–449, 1990.
4. Wu MJ, Kumar KS, Kulkarni G, Kaiser H: Multiple myeloma in naproxen-induced acute renal failure. N Engl J Med 317:170–171, 1987.
5. Hamblin TJ: The kidney in myeloma. Br Med J 292:2–3, 1986.
6. Vane JR, Botting RM: A better understanding of anti-inflammatory drugs based on isoforms of cyclooxygenase (Cox-1 and Cox-2). Adv Prostaglandin Thromboxane Leukotriene Res 23:41–48, 1995.
7. Palmer BF: Renal complications associated with use of nonsteroidal anti-inflammatory agents. J Invest Med 43:516–533, 1995.
8. Murray MD, Black PK, Kuzmik DD, Haag KM, Manatunga AK, Mullin MA, Hall SD, Brater DC: Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. Am J Med Sci 310:188–197, 1995.
9. Perneger TV, Whelton PK, Klag MJ: Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 331:1675–1679, 1994.